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(FILE 'HOME' ENTERED AT 12:22:58 ON 28 DEC 2004)

FILE 'REGISTRY' ENTERED AT 12:24:06 ON 28 DEC 2004
E FORMOTEROL/CN

L1 1 S E3

FILE 'CAPLUS' ENTERED AT 12:24:36 ON 28 DEC 2004

L2 694 S L1 OR FORMOTEROL OR OXIS OR EFORMOTEROL
L3 61 S L2(L) (WATER OR AQUEOUS OR BUFFER OR SOLUTION OR LIQUID)
L4 23 S L3 NOT PY>=2001
L5 32 S L2(L) (WATER OR AQUEOUS OR BUFFER)
L6 11 S L5 NOT PY>=2001

FILE 'USPATFULL, USPAT2' ENTERED AT 12:30:47 ON 28 DEC 2004

L7 114 S L6

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L7 ANSWER 3 OF 114 USPATFULL on STN
ACCESSION NUMBER: 2000:157467 USPATFULL
TITLE: Active substance concentrate with formoterol, suitable
for storage
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EXEMPLARY CLAIM:	1	
LINE COUNT:	430	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a formoterol active substance concentrate suitable for storage, in the form of a solution or suspension for use in inhalers for inhalation or nasal therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM The present invention relates to a propellant-free, active substance concentrate suitable for storage containing **formoterol**, for use in inhalers for inhalation or nasal therapy.

SUMM **Formoterol** is an anilide of formula I derived from adrenaline and is used as a β .sub.2 -stimulator in inhalation therapy of respiratory diseases, particularly for the treatment of bronchial asthma. In patients with reversible obstructive respiratory diseases, **formoterol** has a bronchodilatory effect. Only 1-3 minutes after inhalation the effect sets in and the bronchodilatory effect is still significantly present after 12 hours. **Formoterol** inhibits the release of leukotrienes and other messenger substances involved with inflammation, such as histamines. In addition, **formoterol** may bring about a hyperglycaemic activity. ##STR1##

SUMM In the past it has been found that liquid aerosol formulations of **formoterol** are not suitable for use in inhalers intended for ambulatory inhalation treatment since **formoterol** cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time. For this reason, **formoterol** has previously only been used in powder form for inhalation therapy.

SUMM The present invention relates to a liquid active substance concentrate containing **formoterol** in the form of its free base or in the form of one of the pharmacologically acceptable salts or addition products (adducts) thereof as active substance. The preferred salt is **formoterol** fumarate whilst the preferred addition product is a hydrate of **formoterol**. In the wider context of this specification, the term **formoterol** refers both to the free base according to formula I and also to salts and other addition products of **formoterol** unless otherwise specified or clearly stated in the context.

SUMM The active substance concentrate according to the invention refers to solutions or suspensions in which **formoterol** is dissolved or suspended in highly concentrated form in a pharmacologically suitable

fluid and which are characterised in that the active substance, **formoterol**, can be stored therein for a period from several months possibly up to several years without any deterioration in the. . .

SUMM The term "active substance concentrate" denotes a solution or suspension of an active substance in which the active substance, **formoterol**, is present in highly concentrated form in a pharmacologically acceptable liquid as a solution or suspension. Suspensions are preferred as. . .

SUMM . . . enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted. According to the invention the **formoterol** concentration in the active substance concentrate is between 10 mg/ml and 500 mg/ml. Preferably, the minimum concentration is at least. . . mg/ml and 400 mg/ml, particularly between 250 mg/ml and 350 mg/ml. The concentration data relate to mg of free base **formoterol** per ml of active substance concentrate.

In the case of **formoterol** salts or the addition compounds thereof, the concentration data should be converted according to the free base.

SUMM . . . of polar solvents or suspension agents are e.g. dimethylsulphoxide or compounds which contain hydroxyl groups or other polar groups, e.g. **water** or alcohols--particularly ethanol, isopropylalcohol, glycols, especially propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycoether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters etc.

SUMM Examples of protic liquids, which are the most preferred solvents or suspension agents in the context of the invention, are **water**, **aqueous** saline solutions with one or more pharmacologically acceptable salt(s), ethanol or a mixture thereof.

SUMM In the case of **aqueous** ethanol mixtures, the ratio by volume of ethanol to **water** or to the **aqueous** saline solution is between 5:95 and 99:1, preferably between 40:60 and 96:4, most preferably between 75:25 and 96:4. A particularly. . .

SUMM . . . administration. Saline solutions are preferably used for suspension concentrates. The addition of the salt significantly reduces the dissolving power of **water** for the active substance or substances, so as to achieve a stabilising effect on the suspended particles. If desired, saturated. . . salt depends on the precise composition of the solvent or suspension agent and its ability to dissolve the active substance. **Formoterol** should be present in dissolved form in an amount of less than 0.5% by weight, preferably less than 0.1% by weight, in **aqueous formoterol** suspensions in the sense of the active substance concentrate according to the invention, these amounts being based on the total amount (weight) of **formoterol**. However, if the amount of dissolved material is above the specified levels, it can be reduced to below these levels. . .

SUMM . . . be added to the solvent or suspension agent. Co-solvents are suitable for increasing the solubility of additives and optionally the **formoterol**.

SUMM . . . any pharmacologically suitable and therapeutically useful substance which is not an active substance but can be formulated together with the **formoterol** in the pharmacologically suitable solvent or suspension agent in order to improve the qualitative properties of the active substance concentrate. . .

SUMM . . . in combination with a complexing agent, leads to improvement in the stability (shelf life) of some solutions or suspensions containing **formoterol**, particularly if they contain ethanol as solvent.

SUMM If the **formoterol** is present in the active substance concentrate according to the invention as a suspension, the particles are preferably formulated in. . .

SUMM The active substance concentrate according to the invention has the advantage that **formoterol** can be formulated in such a way as to remain stable over a fairly long period of time. It is. . . substantially from the pH of the pharmaceutical preparation which is to be administered, if this ensures more stable storage of **formoterol**.

SUMM In order to obtain the formulation for administration, the

SUMM **formoterol** active substance concentrate is diluted to 0.9 mg/ml to 1.5 mg/ml, for example, with the diluent. Particularly preferred diluents are **water**, **aqueous** saline solutions with one or more pharmacologically acceptable salts, ethanol or a mixture thereof. In the case of **aqueous** ethanol mixtures, the ratio by volume of ethanol to **water** or to the **aqueous** saline solution is between 5:95 and 99:1, preferably between 40:60 and 96:4, most preferably between 75:25 and 96:4. A particularly. . .

SUMM Optionally, the diluent may contain a **buffer** substance, e.g. trisodium phosphate, disodium hydrogen phosphate, sodium dihydrogen phosphate, Na-EDTA, EDTA, mixtures thereof and other substances known from the. . . dihydrogen phosphate, disodium hydrogen phosphate, trisodium hydrogen phosphate, potassium dihydrogen phosphate, potassium hydrogen phosphate, tripotassium hydrogen phosphate, and mixtures thereof. **Buffer** substances are particularly beneficial when the active substance concentrate suitable for storage according to the invention has a pH which. . . desired for the application, e.g. when this increases the stability of the active substance during storage. In this case the **buffer** substance is present in the diluent in a concentration such that, after mixing the active substance concentrate with the diluent, . . .

DETD 5 mg of **formoterol** (particle size: 5 μ m) are formulated as a suspension with 0.015 ml of **water** for storage. A pH of 5.0 is obtained by the addition of fumaric acid.

DETD For administration by inhalation, the suspension is diluted with 4.5 ml of a 1:1 solution of **water**/ethanol (v/v), the diluted solution containing 0.45 mg of benzalkonium chloride and 2.25 mg of Na-EDTA and being adjusted to a. . .

DETD 5 mg of **formoterol** (particle size: 5 μ m) are formulated as a suspension for storage with 0.015 ml of a 20% by weight **aqueous** NaCl solution. The pH is adjusted to 5.0 by the addition of fumaric acid.

DETD For inhalation, the suspension is diluted with 4.5 ml of a 1:1 solution of **water**/ethanol (v/v), the dilute solution containing 0.45 mg of benzalkonium chloride and 2.25 mg of Na-EDTA and being adjusted with HCl. . .

DETD In an **aqueous** solution with a pH of 5.0, **formoterol** breaks down to 10% at 40° C. within only 3 months. In a comparable suspension, no breakdown of any kind. . .

CLM What is claimed is:

1. Propellant-free active substance concentrate suitable for storage containing **formoterol** in the form of its free base, one of the pharmacologically acceptable salts thereof or one of the addition products thereof as the active substance, in a pharmacologically acceptable solvent or suspension agent, wherein the concentration of **formoterol** is between about 75 mg/ml and about 500 mg/ml.
2. Active substance concentrate according to claim 1, characterised in that the concentration of **formoterol** is between about 100 mg/ml and about 400 mg/ml.
3. Active substance concentrate according to claim 2, characterised in that the concentration of **formoterol** is between about 250 mg/ml and about 350 mg/ml.
6. Active substance according to claim 1, characterised in that the solvent or suspension agent is **water**, an **aqueous** saline solution, ethanol or a mixture thereof.
7. Active substance concentrate according to claim 6, characterised in that the **aqueous** saline solution is a sodium chloride solution.